Bristol and the Brain

Jeremy Henley, Professor of Molecular Neuroscience in the Department of Anatomy, considers that the last great frontier of science is whether the brain can understand itself. Here he gives us an insight into just how difficult that might be.

THE FINAL FRONTIER

In addition to the everyday housekeeping functions that are necessary to keep us alive, the brain dictates what we learn and remember and this, in turn, controls what we do and who we are. The organ that performs all of these tasks is a squishy, wrinkly, rather ugly lump of fatty-looking tissue that sits in a fluid-filled cavity in our head.

> The human brain has about 100 billion neurons – about a tenth of the total number of cells in the brain

Over the past 100 years, the areas of the brain that specialise in a wide range of complex control functions have been identified. Many of the pathways that carry the vast amount of communication and the unimaginable quantities of information that are passed, forward and backwards, between different areas have now been mapped. Furthermore, we know that the human brain has about 100 billion neurons (the cells that actually process information), but these represent only about a tenth of the total number of cells in the brain. The rest are various specialised types of support cells.

The general mechanisms by which information is passed from one neuron to another through specific structures called 'synapses' are now well characterised. Individual neurons may possess many thousands of synapses. Synapses consist of closely apposed, highly specialised membranes. The *pres*ynaptic membrane is the point from which information is passed forward to the next cell. The *post*synaptic membrane is the corresponding, but very different, specialised membrane on the neuron receiving information. Proteins called 'receptors' in the postsynaptic membrane receive the signals released from the presynaptic membrane. The process of information transfer between the cells is called 'synaptic transmission'.

Despite the complexity of this system, in the past decade or so there has been rapid progress towards identifying many of the proteins inside neurons that come together to form synapses and which can be modified to facilitate or depress the effectiveness of synaptic transmission. The general term used to cover such changes is 'synaptic plasticity', and it is our goal to further the understanding of the fundamental molecular processes that underlie synapse development and plasticity. These are important processes since they are believed to provide the cellular basis for how we learn and remember.

> AMPA receptors represent an important target for drug design and development

Work in my lab focuses on some of the key proteins that are crucial for receiving information at the postsynaptic membrane. In particular, we are interested in proteins called AMPA receptors. We are especially interested in how these proteins are delivered to the postsynaptic membrane and how their function, once there, is regulated. Since AMPA receptors mediate the overwhelming majority of stimulatory neurotransmission in the brain, understanding the fundamental properties of these receptors is therefore of interest in its own right. Furthermore, since AMPA receptors have been implicated in ➜ many neurodegenerative disease states and their prolonged activation can lead directly to neuronal cell death, AMPA receptors represent an important target for drug design and development.

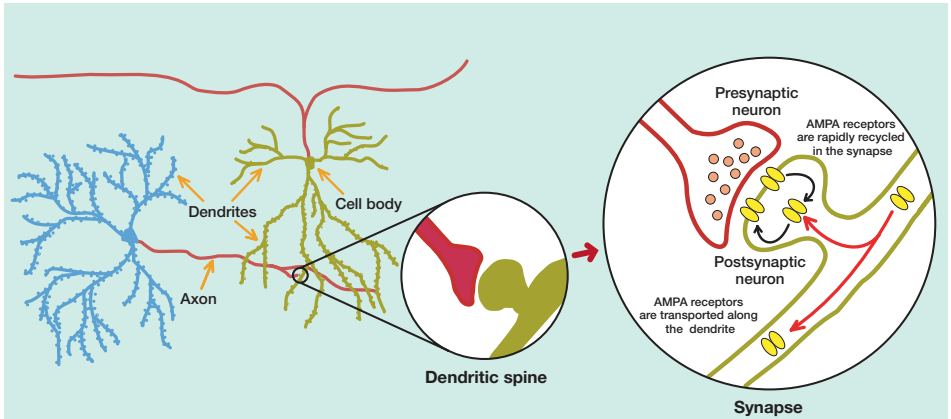

Diagram: Andrew Doherty

Neurons possess a large, branching network of processes called dendrites, that bring incoming information into the cell body. The dendrites are covered in small bulbous structures known as 'spines'. These spines are the sites of neuronal communication, the synapses, where the axon of one neuron (the output) meets the dendrite of another neuron. Understanding the mechanisms that control the movement of receptors at synapses is crucial in understanding how neurons work. Rapid recycling mechanisms result in a dynamic system that can respond to different stimuli. Ultimately, such processes may form the basis of our ability to learn and remember.

Until quite recently, it was believed that AMPA receptors were relatively immobile proteins that sat in the postsynaptic membrane waiting to receive signals. However, the group's recent findings indicate that this is not the case. For example, we were the first group to demonstrate the now widely cited phenomenon of rapid, continuous AMPA receptor 'recycling' at the postsynaptic membrane. Contrary to previous understanding, AMPA receptors sit in the membrane for only 5-10 minutes at a time. They are then taken inside the cell – internalised – where they are either modified in some way or are degraded and broken up, or they are sent straight back to the membrane.

> AMPA receptor movement is analogous to a postal system

At first sight that seems a great waste of energy because it takes a lot of effort for these proteins to be internalised. So why do it? The answer we came up with is that it is to do with inertia. If you want to modify these synapses very quickly, i.e. transmit a signal across the synapse, if the proteins were sitting well anchored in the membrane it would be quite difficult to change the number of receptors available. However, if you have a dynamic system it is quite easy to increase the number of receptors – all you have to do is block the internalisation part and, conversely, if you want to decrease the number you just internalise more. These observations, subsequently repeated and confirmed by other groups, have directly influenced the theories underlying synaptic plasticity.

In related experiments we have tagged AMPA receptors with a variety of fluorescent markers so that we can observe what happens to them in living neurons. This approach allows the non-invasive monitoring of AMPA receptor movement to begin to answer questions such as: 'Where do new AMPA receptors that are rapidly inserted into the postsynaptic membrane come from?'. For example, are they stored inside the cell close to synapses awaiting a signal to be inserted into the postsynaptic membrane, or do they wander about aimlessly within the cell until they are caught by a synapse that requires additional receptors? Our current results suggest the latter possibility is more likely. We are therefore working towards the idea that AMPA receptor movements from the location where they are made to their final destination is analogous to a postal system.

The AMPA receptor package has to be sent to a specific address at a certain time and the process requires a series of hierarchical sorting, transport and delivery steps. These steps are likely to be mediated by proteins that bind to, label, transport and retain the AMPA receptor package. Some of these may be fairly generic – to tell the cell that AMPA receptors need to be transported away from the cell body and directed to the cell membrane, for example. Others are likely to be highly specific, such as proteins that retain certain kinds of AMPA receptor at specific synapses, but only do so under a particular set of conditions.

Unravelling the complexity of this delivery system is our major challenge for the future. ■

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